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**A Comparison of the Treatment Recommendations for Neurogenic Lower Urinary Tract Dysfunction in the National Institute for Health and Care Excellence, European Association of Urology and International Consultations on Incontinence Guidelines.**

**ABSTRACT:**

**AIMS:** Healthcare guidelines are an important vehicle in establishing up-to-date evidence based medicine (EBM) in clinical practice. Due to varying development processes, clinical guidelines created by different institutions can often contain contrasting recommendations. This can have implications for optimal and standardised patient care across management settings.

**METHODS:** The similarities and differences of treatment recommendations made in the National Institute for Health and Care Excellence (NICE), The European Association of Urology (EAU) and the International Consultation on Continence (ICI) guidelines for neurogenic lower urinary tract dysfunction (NLUTD) were assessed.

**RESULTS:** The guidelines generally agree on their approach to conservative management, including behavioural therapies and catheterisation techniques. There was discrepancy on the benefit of using an alpha blocker in NLUTD and bladder outlet obstruction (BOO) and administering Botulinum toxin A (Onabotulinum-A) in NLUTD. The highest degree of divergence was seen in recommendations for surgical treatments, where the EAU made gender-specific recommendations, and gave continent urinary diversion higher preference than given in the NICE and ICI guidelines.

**CONCLUSIONS:** In the absence of high-quality clinical evidence, many of the recommendations made across all three guidelines are based on expert opinion. NICE, the EAU and ICI have similarities but they place differing emphasis on costs and expert opinion, which translated in notably different recommendations. It is evident that increased research efforts, possibly in the form of prospective registries, pragmatic trials and resource utilisation studies are necessary to improve the underlying evidence base for NLUTD, and subsequently the strength and concordance of recommendations across guidelines.

**MAIN TEXT:**

**BACKGROUND**

Disturbance to the normal micturition process emanating from neurological damage or disease is known as neurogenic lower urinary tract dysfunction (NLUTD). The underlying neurological disease differentiates NLUTD from those suffering from idiopathic overactive bladder (OAB). NLUTD encompasses a breadth of neurological aetiologies, including stroke, spinal cord injuries (SCI), multiple sclerosis (MS) and Parkinson's disease (PD). Patients that fall under the umbrella term of NLUTD are notably unique in urological symptoms and risk profile due to differences in underlying condition (including stage and severity) and location of neurological lesion.

There are myriad treatment options for the management of NLUTD, supported by a substantial evidence base. The evidence is however dominated by observational studies and clinical studies with weak methodological design. Clinical guidelines aid physicians in making optimal treatment choices through encapsulating the plethora of dynamic scientific research and expert opinion into easy to follow recommendations. The most prominent NLUTD guidelines are produced by the National

Institute for Health and Care Excellence (NICE), the European Association of Urology (EAU) and the International Consultation on Continence (ICI).<sup>1,2,3</sup>

Due to variations in development processes, clinical guidelines by different institutions can often contain contrasting recommendations. This can be confusing for healthcare professionals and patients when devising management strategies, and can affect standardisation of care.<sup>4</sup> To assess the concordance of prominent guidelines for NLUTD; we assessed the similarities and differences of treatment recommendations made in the NICE, EAU and ICI guidelines.

## **GUIDELINES**

We included the three most prominent guidelines for NLUTD from recognised institutions within the UK, Europe and internationally.

NICE provides evidence-based clinical care guidance for the UK National Health Service (NHS).<sup>5</sup> The guidelines entitled 'urinary incontinence related to neurological disease' are applicable to adults and children. The guidelines are updated periodically, and the most recent update was in 2012. NICE uses a modified version of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to rate the quality of evidence and uses the wording of recommendations to reflect the strength of the recommendation.

The EAU strives to improve urological practice, research and education across Europe.<sup>6</sup> They provide guidelines on a wide range of urological topics, including for NLUTD. The guidelines are updated annually, with the most recent edition being in 2017. The EAU present levels and grades of recommendations using a modified version of the Oxford Centre for Evidence-based Medicine system (OCEBM 2009).

The International Consultation on Urologic Disease (ICUD) is a non-governmental organisation registered with the World Health Organisation (WHO). The ICI is a sub-committee of the ICUD, tasked with developing recommendations with worldwide relevance for lower urinary tract dysfunction (LUTD).<sup>7</sup> Their guidelines entitled 'neurologic urinary and faecal incontinence' are based on evidence and conclusions drawn at the sixth annual ICI conference. The ICI uses a modified version OCEBM 2011. They provide evidence levels for conclusions drawn from the literature and grades for recommendations.

## **RESULTS**

### **BEHAVIOURAL INTERVENTIONS**

Whilst no graded recommendations are made in the EAU guidelines, behavioural interventions are advocated in both the NICE and ICI guidelines, although recommendations are based on a lack of clinical evidence.

NICE and the ICI broadly agree on their recommendations for individuals with cognitive impairment (table 1). All three guidelines agree on the use of pelvic floor muscle training (PFMT) in combination with electrical stimulation or biofeedback, however NICE only advocate this technique in SCI or MS, and the EAU recommend it only in MS patients (table 1). The ICI and EAU endorse expression

techniques such as the Credé and Valsalva manoeuvres, only if proven urodynamically safe, however both guidelines also stress that the manoeuvres can be potentially hazardous.

### ORAL PHARMACOLOGICAL MANAGEMENT

Antimuscarinics are the preferred pharmacological treatment for neurogenic detrusor overactivity (NDO); although NICE make a weaker recommendation for progressive brain conditions (table 2). All guidelines advise cautionary use of these drugs due to the increased possibility of adverse effects such as cognitive dysfunction, urinary tract infections (UTIs) and constipation. The ICI and NICE guidelines particularly express concern of use in patients with pre-existing cognitive impairment. The EAU suggests employing antimuscarinics in combinations in order to maximise outcomes (table 2).

The ICI and EAU recommend  $\alpha$ -blockers for bladder outlet obstruction (BOO) resistance. Conversely,  $\alpha$ -blockers are recommended against in the NICE guidelines for bladder emptying problems, as they are deemed not cost-effective (table 2).

### MINIMALLY INVASIVE TREATMENTS

The EAU recommends alternative (non-oral) routes of administration of antimuscarinic drugs. Both the ICI and NICE do not provide graded recommendations for alternative forms of antimuscarinic administration.

On account of high-level evidence, the EAU and NICE advocate Onabotulinum-A in NDO as a consequence of SCI and MS (table 3). In contrast, the ICI recommends Onabotulinum-A for NDO indiscriminate of underlying neurological condition (table 3). The ICI again diverges from EAU and NICE when it recommends Onabotulinum-A for detrusor sphincter dyssynergia (DSD) in SCI (table 3).

The ICI guidelines provide grade C/D recommendation for electrical neuromodulation techniques including, however both the EAU and ICI agree there are limited reports proving efficacy (table 3).

### CATHETERS AND APPLIANCES

All guidelines recommend intermittent catheters (IC) over indwelling catheter (IDC) due to increased complications such as renal problems and bladder stones associated with the latter (table 4), though the ICI guidelines do not completely preclude its use (table 4). NICE also recognise that in some instances the choice of management technique is limited by what the patient can manage.

When considering appliances, NICE recommend the use of catheter valves over drainage bags. The ICI and EAU guidelines advocate the use of condom catheters with a collection device in men (although the EAU do not provide a graded recommendation) (table 4).

### SURGICAL PROCEDURES

All guidelines recommend augmentation using intestinal segment in refractory NDO (table 5). NICE consider augmentation to be more cost-effective than Onabotulinum-A in patients likely to benefit from treatment for more than 10 years.

The EAU make gender specific recommendations for autologous sling use in SUI and artificial urinary sphincter (AUS) in neurogenic sphincter deficiency. NICE differ from the other guidelines when they

only recommend AUS use after autologous sling procedures have failed, due to the high rates of re-operation in ten years (table 5). The ICI make further recommendations for stress urinary incontinence (SUI) that are not covered by the other guidelines. They also present bladder neck closure as a last resort if all possible alternatives are unsuitable or have failed to relieve symptoms (table 5).

According to the EAU, continent cystostomy is the preferable urinary diversion technique in refractory NLUTD. Conversely, NICE only provide recommendations for ileal conduit diversion (table 5).

The ICI recommend urethral stenting or surgical sphincterotomy for patients with DSD, in whom IC is not an option. Sacral rhizotomy in conjunction with sacral anterior root stimulation (SARS) is given a graded recommendation by the ICI (and advocated in the EAU guidelines), in highly selected individuals (table 5).

## **DISCUSSION**

Clinical guidelines are an important vehicle in establishing up-to-date evidence based medicine (EBM) in clinical practice. Adequate management in NLUTD offers benefits to the patient in terms of protection of the upper urinary tract, reduction in the rate of adverse sequelae and promotion of good quality of life (QoL).<sup>9</sup> Additionally, unnecessary costs to the healthcare system can be avoided. Due to varying development processes, clinical guidelines can contain discordant treatment recommendations, which can cause unwarranted variation in care across practices. Despite many similarities, recommendations made in the NICE, EAU and ICI guidelines also diverged for some therapies.

The guidelines generally agree on their approach to conservative management, including for behavioural therapies and catheterisation techniques. The recommendations for behavioural therapy were mostly based on expert opinion. NICE made their recommendations using evidence from the general elderly population, on the basis that no relevant evidence exists for neurological patients.

When considering oral pharmacotherapy, all three guidelines place antimuscarinics as first line for NDO. Level 1 in the ICI evidence states tolterodine, propiverine, trospium and controlled-release oxybutynin have significantly less side effects compared to immediate release oxybutynin. Due to the lack of evidence differentiating antimuscarinics, NICE recommend balancing side effect profile with cost, rather than advocating the use of one drug over another.

The ICI and NICE recommend further research into the use of newer antimuscarinics in NGB. It is interesting to note that although the ICI guidelines were published five years after the NICE guidelines; the same recommendation is made, indicating that little progress has been made in the way of this particular research. Despite highlighting the potential adverse effects of these drugs, none of the guidelines acknowledges the particular concern of use in progressive neurological conditions (e.g. PD and MS). Even if notable impairment does not already exist, the blood brain barrier (BBB) can become compromised, increasing the ability of antimuscarinics to bind to the M1 receptors in the brain and cause cognitive side effects.<sup>10,11,8</sup>

The guidelines contain contrasting recommendations on alpha-blockers and Onabotulinum-A. Although some evidence exists demonstrating efficacy of alpha-blockers in NLUTD with BOO, the need for large randomised controlled trials (RCTs) remains.<sup>12</sup> Despite this, alpha-blockers are advocated for

use in the EAU and ICI guidelines. Onabotulinum-A is only licensed for NDO in SCI and MS due to the paucity of adequate research in other neurological conditions. The ICI guidelines still recommend Onabotulinum-A in all patients with NDO, regardless of underlying aetiology, thus it is evident that the EAU and NICE guidelines more accurately reflect the evaluated patient population. In the absence of high quality clinical evidence, recommendations for alpha-blockers and Onabotulinum-A were primarily reliant upon expert opinion.

Disparities were most apparent in surgical treatments. One major difference between the EAU guidelines and the other guidelines were some gender-specific recommendations. Male autologous slings are relatively new interventions, with consequently less data supporting their use than female autologous slings.<sup>13</sup> For this reason, use in males is not advocated in the EAU guidelines. On the other hand, AUS is not recommended in females, as physiological barriers introduce technical difficulties in implantation.<sup>14</sup> All guidelines also differed in recommendations for urinary diversion. Whereas continent cystostomy is advocated in the EAU guidelines, NICE recommend ileal conduit diversion. The ICI do not advocate any one kind of diversion technique, which is perhaps most suitable, as superiority of one type of urinary diversion in terms of functionality and health related quality of life (HRQOL) has not yet been proven.<sup>15</sup> The discrepancy between the NICE and EAU guidelines is again most likely because of differing expert opinion.

Dissimilarities arose as a result of the differing interpretation of the underlying evidence base, varying considerations given to cost, and the weight given to expert opinion. Since the ICI guidelines attempt worldwide relevance, they were most comprehensive. For example, the guidelines provide extensive recommendations for patients with SUI, considering treatments that were not assessed in the NICE or EAU guidelines. An advantage of the NICE guidelines was the well-integrated economic evaluation, which aims to improve national healthcare efficiency in the UK. As a result, certain recommendations diverged from what is recommended by the EAU and ICI, for example, the option to introduce bladder augmentation earlier than Onabotulinum-A in the treatment pathway for a subset of patients. Due to their broad country remit, cost assessment and/or consideration of resource utilisation is not possible for the EAU and ICI guidelines. The EAU guidelines were adequately detailed, and considered a broad range of treatments, however they lacked graded recommendations for behavioural management.

In the absence of high-quality clinical evidence, many of the recommendations made across all three guidelines are based on expert opinion. In the EBM hierarchy, expert opinion is assigned the lowest level, as it can be subject to bias. At present, much of the clinical evidence that does exist for NLUTD focuses on SCI and MS, which may not be generalizable to the wider neuro-urological patient population, especially progressive neurological conditions.<sup>16</sup> Filling the research gap is not easy, as conducting RCTs in the vulnerable NLUTD population can be impractical. In order to strengthen recommendations, increased research effort should be focused on collecting prospective registries or conducting pragmatic trials at centres managing a diverse range of neurological conditions.

## **CONCLUSIONS**

NICE, the EAU and ICI guidelines are quite similar, but they do provide differing emphasis on costs and expert opinion, which translated in notably different recommendations. This is not surprising in the absence of high-quality clinical evidence for NLUTD. It is evident that increased research efforts are necessary to improve the underlying evidence base for NLUTD, and subsequently the strength and concordance of recommendations across guidelines. This will enhance the care that NLUTD receive,

and ultimately improve patient outcomes. In addition to this, integrating cost-effectiveness analyses may improve efficiencies.

### **TABLE LEGENDS**

Table 1: Behavioural management recommendations for NLUTD in the National Institute of Health and Care Excellence, European Association of Urology, and the International Consultations on Incontinence guidelines

Table 2: Oral pharmacotherapy recommendations for NLUTD in the National Institute of Health and Care Excellence, European Association of Urology, and the International Consultations on Incontinence guidelines

Table 3: Minimally invasive treatment recommendations for NLUTD in the National Institute of Health and Care Excellence, European Association of Urology, and the International Consultations on Incontinence guidelines

Table 4: Catheter and appliance recommendations for NLUTD in the National Institute of Health and Care Excellence, European Association of Urology, and the International Consultations on Incontinence guidelines

Table 5: Surgical procedure recommendations for NLUTD in the National Institute of Health and Care Excellence, European Association of Urology, and the International Consultations on Incontinence guidelines

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